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Double-blind Comparison of Tolamolol, Propranolol, Practolol, and Placebo in the Treatment of Angina Pectoris

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Summary

Forty-two patients with angina pectoris have completed a randomized, double-blind trial comparing tolamolol 100 mg and 200 mg with propranolol 80 mg, practolol 100 mg, and placebo, all given three times a day. Tolamolol 200 mg thrice daily was found to be equivalent to propranolol 80 mg thrice daily in anti-anginal efficacy. Anginal attack rates and trinitrin consumption were significantly reduced by all active treatments as compared with the placebo but tolamolol and propranolol were the most effective. Tolamolol 200 mg thrice daily was most effective in reducing blood pressure, while propranolol was most effective in reducing the resting heart rate.

All treatments except the placebo significantly increased the amount of exercise which could be performed before angina appeared (exercise work), while tolamolol 200 mg thrice daily significantly reduced Robinson's index when compared with all other active agents. The degree of S-T segment depression induced by exercise was significantly lessened by both tolamolol and propranolol but not by practolol or placebo. There was no difference in patient preference between tolamolol and propranolol but tolamolol at both dose levels was preferred to practolol.

Both tolamolol and propranolol are potent adrenergic beta-receptor antagonists and equal in anti-anginal efficacy but tolamolol has the advantage of being cardio-selective. It is superior to practolol.

Introduction

Adrenergic beta-receptor antagonists are well established in the treatment of angina pectoris. Propranolol was the first of these to be clinically accepted and is probably the standard reference agent used (Gillam and Prichard, 1965; Grant *et al.*, 1966; Wolfson *et al.*, 1966). It is not cardioselective, however, and may predispose to bronchospasm (McNeill, 1964; Stephen, 1966) and reduce myocardial contractility with the risk of cardiac failure (Sowton and Hamer, 1966). A selective action on

cardiac beta-adrenergic receptors reduces the incidence of bronchospasm and myocardial depression and is a desirable feature of adrenergic beta-receptor antagonists for angina pectoris (Dollery *et al.*, 1969; Fitzgerald, 1969; Miller *et al.*, 1974). Practolol is a cardioselective adrenergic beta-receptor antagonist with intrinsic sympathomimetic activity (Dunlop and Shanks, 1968). It is, however, less effective than propranolol in angina pectoris (Sandler and Clayton, 1970; Prichard *et al.*, 1971) and though it is less likely to produce bronchospasm and the so-called negative inotropic effect—namely, myocardial depression—these have been induced (Wiseman, 1971). In addition side effects have included systemic lupus erythematosus (Raftery and Denman, 1973), psoriasis-like rashes (Felix and Ive, 1974), and ocular changes (I.C.I., 1974).

Composition of tolamolol (UK-6558-01); 1-[2-(4-carbamoylphenoxy)ethylamino]-3-(2-methylphenoxy) propan-2-ol hydrochloride.

Tolamolol (UK 6558-01) (see fig.) is a new adrenergic beta-receptor antagonist without intrinsic sympathomimetic activity which is cardioselective in animals (Augstein *et al.*, 1973; Adam *et al.*, 1974). In volunteers (Briant *et al.*, 1973) tolamolol and practolol were similar in cardioselectivity, whereas the potency of tolamolol was similar to that of propranolol in antagonizing exercise-induced tachycardias (Adam *et al.*, 1973). In man tolamolol has a dominant effect in reducing the heart rate, the so-called negative chronotropic effect, and only a slight negative inotropic action (Hillis *et al.*, 1974). A preliminary report (Sood and Havard, 1973) in patients with angina pectoris showed an increase in exercise tolerance equivalent to that found with propranolol.

To assess the clinical efficacy of tolamolol a double-blind evaluation comparing it with propranolol and practolol has been undertaken.

Patients and Methods

SELECTION AND ENTRY OF PATIENTS

Patients with exercise-induced angina were selected. They were excluded if the angina was associated with anaemia (haemoglobin less than 13 g/dl), valvular heart disease, cardiac failure, obstructive airways disease, cardiac infarction in the previous three months, hypertension (fifth-point resting diastolic pressure over 100 mm Hg), diabetes, or thyroid disease. In all the patients the angina had been stable for more than three months and all showed electrocardiographic

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abnormalities either at rest (World Health Organization, 1959) or on exertion (Thadani *et al.*, 1973). A standard x-ray picture showed no cardiomegaly or raised pulmonary venous pressure. No other drugs were used except for trinitrin. To be included in the study the patients had to have more than four anginal attacks a week though five patients subsequently had fewer on the placebo run-in period.

All the patients were clearly informed of the nature of the study and all gave written consent without inducement (Ormrod, 1968). Forty-seven patients entered the trial. One patient after benefiting from practolol developed a severe bradycardia on 100 mg tolamolol thrice daily. He was withdrawn from the trial but continued well on 50 mg thrice daily. One patient withdrew for domestic reasons. Two patients sustained a cardiac infarct; one died within six hours in cardiogenic shock when on 200 mg tolamolol thrice daily, and the other survived the initial anterior infarct while on 100 mg thrice daily but died during convalescence when receiving no drugs. One patient developed crescendo angina while on tolamolol 100 mg thrice daily and died two weeks later from cardiac infarction while on propranolol. The expected yearly mortality rate is about 4% (Kannel and Feinleib 1972), and as our trial lasted 10 months with each patient we believe that these deaths represent the natural history of angina pectoris. These patients were excluded from the analysis.

Of the 42 patients completing the trial 32 were men aged 36-70 (mean 55) years and 10 were women aged 46-68 (mean 56) years.

DOSAGE AND REGIMEN

Patients were seen fortnightly. After trinitrin alone for two weeks each patient received placebo on a single-blind basis for four weeks. This period enabled the effect of increased doctor interest, by itself leading to improvement (Beecher, 1955), to be stabilized and gave the patients time to familiarize themselves with record cards and exercise testing. They were then allocated to five fully randomized monthly treatment periods—A, tolamolol 200 mg thrice daily; B, tolamolol 100 mg thrice daily; C, propranolol 80 mg thrice daily; D, practolol 100 mg thrice daily; and E, placebo, which consisted of starch lactose. All the preparations were in identical capsules, each dose being two capsules. Each drug course was checked by counting the capsules and trinitrin tablets; blood and urine levels were not estimated. Periodic chemical analysis confirmed the contents of the capsules. Trinitrin was supplied in dark glass bottles of 100 tablets replenished monthly and stored out of direct light and with the minimum cotton-wool filling (*Cardiology Today*, 1973).

ASSESSMENT

The patients attended the ischaemic heart disease clinic at King's College Hospital or Brook General Hospital. All the observations were made by one of us (G.J.) on the same day of the week and, so far as possible, at the same time of day. As well as the drugs, advice was given on life style and work during the run-in period with emphasis on the benefits of a full, active life. The total duration of the trial was 10 months.

During the run-in period a detailed case history was taken. All previous therapy was discontinued and general practitioners were asked to telephone if they wished to prescribe other drugs. No benzodiazepines or clofibrate were administered (Sharma and Taylor, 1972). At each examination the attack rate and trinitrin consumption were assessed from the record cards. Trinitrin was used only for attacks of pain, not prophylactically. The drug capsules were taken at 8 am, 2 pm, and 8 pm. The overall monthly attack rate and trinitrin consumption were compared with those in the second two weeks of each period of treatment to assess any carry-over effects. Also at each attendance subjective wellbeing; blood pressure sitting, standing (one minute), and supine (three minutes); and pulse rate (supine) were recorded and a full clinical examination was carried out. Any side effects were noted.

At the end of each four-week period the patient was weighed and exercised. He was then asked to grade the treatment period as good, moderate, or poor. At the end of the trial he stated his drug of choice and received it for long-term assessment.

EXERCISE TEST

The large-muscle-mass exercise test of Kaltenbach (1968) was used as modified and described in detail by Livesley *et al.* (1973). Pre-

cautions were taken to control factors which might have produced errors in evaluation (Andersen *et al.*, 1971). The laboratory temperature was $20^{\circ} \pm 1^{\circ} \text{C}$, the time of day and time after the last capsule dose were as consistent as possible, no patient was allowed to smoke on the day of the test, food was taken at least 90 minutes before the test, the test was postponed if angina had occurred in the previous four hours, and each patient underwent 12-lead electrocardiography before the test. Electrocardiographic radiotelemetry using the V5 position was employed.

Before the trial each patient was exercised three times to assess the reproducibility of the test and to familiarize him with it. The exercise test was continued until the patient developed any anginal pain or was too breathless to continue. The electrocardiograms were analysed by G.J. before the trial code was broken on completion of the whole study.

Results

For brevity we have summarized our results as mean values with the standard error (S.E.) of the mean. Tables of more detailed data are available from G.J. As the data have a non-normal distribution our statistical analysis is based on Friedman's two-way analyses of variance and the ranking test of Tukey.

ANGINAL ATTACK RATE AND TRINITRIN CONSUMPTION

The weekly attack rate and trinitrin consumption for each period of treatment are shown in table I. The carry-over effect has long been a problem with anti-anginal trials but no one has exactly defined the period to allow for. Comparison of our four-week figures with the last two-week figures showed small statistical variations in trinitrin consumption (table II).

Tolamolol at both dose levels and propranolol were highly significantly superior to placebo ($P < 0.001$) in reducing the attack rates, whereas practolol was less significantly effective ($P < 0.05$). No significant difference could be shown between active treatments. Propranolol was slightly more effective in reducing trinitrin consumption, with no significant difference between active treatments. Friedman's test (table III) showed propranolol to have the lowest average rank.

HEART RATE AND BLOOD PRESSURE

The heart rate was estimated from the electrocardiogram, and a standard sphygmomanometer was used for blood-pressure readings. The results are shown in table IV. No difference was shown between sitting, standing, and supine recordings and only sitting recordings are tabulated. The peak-exercise blood pressure was recorded within 10 seconds of ceasing to exercise.

Heart rate and blood pressure fell considerably both at rest and on exertion with all active treatments (table II). Though no significant difference existed between the active treatments tolamolol 200 mg thrice daily produced lower systolic and diastolic pressures at rest. On exertion this dosage of tolamolol was significantly superior to all treatments in reducing the systolic blood pressure. In comparison with the placebo all the active treatments significantly ($P < 0.001$) reduced the resting heart rate and peak exercise heart rate. Tolamolol at both dose levels was significantly superior to practolol ($P < 0.01$) in reducing the resting heart rate but propranolol was significantly superior to tolamolol at both dose levels in reducing the resting heart rate ($P < 0.01$).

The product of systolic blood pressure and heart rate at peak exercise, Robinson's (1967) index, was significantly reduced by all active treatments compared with the placebo ($P < 0.001$), whereas the higher dose level of tolamolol was significantly superior to propranolol ($P < 0.05$) and practolol ($P < 0.001$).

EXERCISE TESTS

In 87 tests the end-point was typical anginal pain and in 153 the end-point was breathlessness. Both groups were assessed independently with regard to exercise time, work done, peak blood pressure, and heart rate. No differences emerged and the combined results are given in table V.

TABLE I—Mean ($\pm$ S.E. of Mean) Anginal Attack Rate and Trinitrin Consumption (Number of Tablets) in Each Treatment Period

	Placebo	Tolamolol 100 mg Thrice Daily	Tolamolol 200 mg Thrice Daily	Propranolol 80 mg Thrice Daily	Practolol 100 mg Thrice Daily
Weekly anginal attack rate in last two weeks ..	12.40 $\pm$ 1.69	9.45 $\pm$ 1.60	8.26 $\pm$ 1.49	8.38 $\pm$ 1.60	10.33 $\pm$ 1.64
Weekly anginal attack rate in four-week period ..	12.38 $\pm$ 1.67	9.48 $\pm$ 1.55	8.36 $\pm$ 1.45	8.19 $\pm$ 1.51	10.00 $\pm$ 1.49
Weekly trinitrin consumption in last two weeks ..	12.23 $\pm$ 1.43	7.38 $\pm$ 1.75	6.07 $\pm$ 1.39	6.48 $\pm$ 1.58	7.69 $\pm$ 1.69
Weekly trinitrin consumption in four-week period ..	9.33 $\pm$ 1.87	7.57 $\pm$ 1.71	6.24 $\pm$ 1.38	6.07 $\pm$ 1.53	7.36 $\pm$ 1.49

TABLE II—Summary of Effects of Treatment Periods (Tukey's Test)

	Tolamolol 200 mg Thrice Daily v. Placebo	Tolamolol 100 mg Thrice Daily v. Placebo	Propranolol 80 mg Thrice Daily v. Placebo	Practolol 100 mg Thrice Daily v. Placebo	Tolamolol 200 mg Thrice Daily v. Propranolol 80 mg Thrice Daily	Tolamolol 100 mg Thrice Daily v. Propranolol 80 mg Thrice Daily	Tolamolol 200 mg Thrice Daily v. Practolol 100 mg Thrice Daily	Tolamolol 100 mg Thrice Daily v. Practolol 100 mg Thrice Daily	Tolamolol 200 mg Thrice Daily v. Practolol 100 mg Thrice Daily
Reduction in attacks in last two weeks ..	P<0.001	P<0.001	P<0.001	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.
Reduction in attacks over four-week period ..	P<0.001	P<0.001	P<0.001	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.
Reduction in trinitrin in last two weeks ..	P<0.01	P<0.01	P<0.001	P<0.01	N.S.	N.S.	N.S.	N.S.	N.S.
Reduction in trinitrin over four-week period ..	P<0.01	P<0.05	P<0.001	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.
B.P. Systolic fall at rest ..	P<0.001	P<0.01	P<0.01	P<0.01	N.S.	N.S.	N.S.	N.S.	N.S.
Diastolic fall at rest ..	P<0.01	N.S.	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fall in systolic B.P. on exertion ..	P<0.001	P<0.001	P<0.001	P<0.001	P<0.05	N.S.	P<0.001	N.S.	P<0.05
Fall in heart rate at rest ..	P<0.001	P<0.001	P<0.001	P<0.001	P<0.01*	P<0.01*	P<0.01	P<0.01	N.S.
Fall in heart rate, peak exercise ..	P<0.001	P<0.001	P<0.001	P<0.001	N.S.	P<0.01*	P<0.05	N.S.	P<0.01
Reduction of Robinson's index ..	P<0.001	P<0.001	P<0.001	P<0.001	P<0.05	N.S.	P<0.001	N.S.	P<0.001
Prolongation of exercise time ..	N.S.	N.S.	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Increase in work done ..	P<0.05	P<0.05	P<0.05	P<0.05	N.S.	N.S.	N.S.	N.S.	N.S.
Decrease in exercise S-T depression ..	P<0.001	P<0.01	P<0.001	N.S.	N.S.	N.S.	P<0.01	P<0.01	N.S.
Patient preference ..	P<0.001	P<0.001	P<0.001	N.S.	N.S.	N.S.	P<0.01	P<0.01	N.S.

* Propranolol superior. N.S. = Not significant at P<0.05.

TABLE III—Friedman's Test on Attack Rate and Trinitrin Consumption

Variable	Treatment	Average	Average Rank	Friedman's χ^2
Weekly attack rate (last two-week average)	Tolamolol 200 mg	8.31	2.69	29.92*
	Tolamolol 100 mg	9.45	2.68	
	Propranolol	8.38	2.36	
	Practolol	10.33	3.21	
	Placebo	12.40	4.06	
Weekly tablet consumption (last two-week average)	Tolamolol 200 mg	6.05	2.64	20.49*
	Tolamolol 100 mg	7.38	2.79	
	Propranolol	6.26	2.51	
	Practolol	7.69	3.18	
	Placebo	9.26	3.88	

* Significant at P<0.001.

All active treatments increased exercise work, which was measured as the product of body weight in kilograms and exercise time in seconds. Only propranolol significantly prolonged the exercise time, while no significant difference existed between the other active treatments.

Some patients on tolamolol at both dose levels and propranolol had their exercise tolerance reduced, and by coincidence there were 13 of them in each group.

ELECTROCARDIOGRAPHIC CHANGES

Comparison of the electrocardiograms taken during the run-in

period with those taken during the double-blind placebo period showed only five patients with a different degree of S-T segment depression on peak exercise

Tolamolol at both dose levels and propranolol were highly significantly more effective than placebo in reducing exercise-induced S-T depression (P<0.001), while tolamolol was also superior to practolol (P<0.01) (tables II, IV). Friedman's test showed the higher dosage of tolamolol to have the lowest mean rank (table VI).

PATIENT PREFERENCE

At the end of each period of treatment the patient graded the agent as good, moderate, or poor and at the end of the trial stated which drug letter he preferred. The results are shown in table VII. Friedman's analysis again showed propranolol to have the lowest mean rank but an equal number of patients preferred tolamolol at both dose levels as preferred propranolol.

SIDE EFFECTS AND TOXICITY STUDIES

Twice during the run-in period and at the end of each month of treatment the haemoglobin level, erythrocyte sedimentation rate, results of liver-function tests, urea and electrolyte levels, antinuclear factor titre, presence of L.E. cells, appearances on urine microscopy, and a 12-lead electrocardiogram were recorded. One patient on practolol developed a rising titre against antinuclear factor, from

TABLE IV—Mean ($\pm$ S.E. of Mean) Changes in Heart Rate and Blood Pressure at Rest and on Exertion

	Placebo	Tolamolol 100 mg Thrice Daily	Tolamolol 200 mg Thrice Daily	Propranolol 80 mg Thrice Daily	Practolol 100 mg Thrice Daily
Heart rate/min { At rest ..	83.17 $\pm$ 1.84	66.45 $\pm$ 1.74	65.12 $\pm$ 1.43	61.07 $\pm$ 1.57	70.79 $\pm$ 1.79
{ On exertion ..	141.88 $\pm$ 2.59	111.33 $\pm$ 2.58	103.41 $\pm$ 2.40	104.24 $\pm$ 2.13	109.60 $\pm$ 2.48
Systolic blood pressure { At rest ..	133.69 $\pm$ 2.38	126.07 $\pm$ 2.76	120.71 $\pm$ 2.69	123.05 $\pm$ 3.82	127.02 $\pm$ 2.75
{ On exertion ..	154.88 $\pm$ 3.59	133.57 $\pm$ 2.87	126.46 $\pm$ 2.48	134.52 $\pm$ 3.00	138.33 $\pm$ 2.46
Diastolic blood pressure at rest* ..	78.3 $\pm$ 1.64	74.88 $\pm$ 1.60	72.80 $\pm$ 1.52	73.33 $\pm$ 1.59	76.19 $\pm$ 1.40

* No appreciable changes occurred in diastolic blood pressure on exercise.

TABLE V—Results of Exercise Tests Expressed as Means $\pm$ S.E. of Means

	Placebo	Tolamolol 100 mg Thrice Daily	Tolamolol 200 mg Thrice Daily	Propranolol 80 mg Thrice Daily	Practolol 100 mg Thrice Daily
Exercise time (s) ..	92.95 $\pm$ 5.64	105.5 $\pm$ 6.79	107.49 $\pm$ 7.90	107.50 $\pm$ 7.12	104.48 $\pm$ 7.90
Work done (kg $\times$ s $\times$ 10 ⁻³) ..	6.70 $\pm$ 0.48	7.64 $\pm$ 0.59	7.73 $\pm$ 0.61	7.71 $\pm$ 0.59	7.52 $\pm$ 0.64
S-T segment depression (mm) ..	1.44 $\pm$ 0.19	0.86 $\pm$ 0.21	0.51 $\pm$ 0.13	0.69 $\pm$ 0.19	1.01 $\pm$ 0.19

TABLE VI—Friedman's Analysis of S-T Segment Changes

	Mean	Mean Rank
Tolamolol 200 mg	0.41	2.39*
Tolamolol 100 mg	0.74	2.82
Propranolol	0.55	2.60
Practolol	0.90	3.26
Placebo	1.25	3.92

* Friedman's χ^2 (4 D.F.) = 23.84; significant at $P < 0.001$.

TABLE VII—Patients' Assessment of Treatment Periods (Figures are Numbers of Patients)

	Tolamolol 200 mg	Tolamolol 100 mg	Propranolol 80 mg	Practolol 100 mg	Placebo
Good	22	19	28	10	6
Moderate	14	15	8	16	11
Poor	6	8	6	16	25

1/20 to 1/40. No other abnormalities were noted. Chest x-ray examination before the study and at the end showed no change in any patient.

Minor side effects such as listlessness, malaise, and cold limbs were reported with all the treatments including the placebo and were always tolerated.

Discussion

Most trials of adrenergic beta-receptor antagonists have been with a fixed dose (Keelan, 1965; Grant *et al.*, 1966), which may fail to allow for individual patient response. This may be partly offset by selecting an adequate dose level of the standard reference agent and using two different doses of the drug under study (Hebb *et al.*, 1968). Our study was designed to compare the clinical efficacy of the new cardioselective agent tolamolol with the reference drug propranolol and the only other clinically available cardioselective drug practolol. The dose selected for propranolol, 80 mg three times a day, is generally effective (Grant *et al.*, 1966; Rabkin *et al.*, 1966; Wolfson *et al.*, 1966; I.C.I., personal communication). Tolamolol was thought to be approximately equipotent with propranolol (50 mg tolamolol = 40 mg propranolol) from studies on animals and volunteers (Adam *et al.*, 1973; Pfizer, 1973). A dose of 100 mg thrice daily was therefore chosen, and a dose of 200 mg thrice daily was also given to assess the effects of increased adrenergic beta-receptor antagonism.

Outpatient trials depend on the patient being trusted to take his medication in the prescribed manner and to keep accurate record cards. Furthermore, prolongation of exercise may not necessarily be recorded as a reduction in the number of anginal attacks (Prichard, 1972). These factors will operate for placebo as well as for active agents and we felt that the patients in this trial followed our instructions accurately and reliably. When they had doubts or problems they were encouraged to telephone, and this rapidly prevented errors. A run-in period of six weeks proved long enough to establish rapport. Record cards and exercise tests were completed accurately.

Broadly speaking, anti-anginal drugs may be evaluated according to subjective or objective criteria.

SUBJECTIVE DATA

The aim of treatment with anti-anginal drugs is to relieve chest-pain, a totally subjective index. The patient's preference for a particular drug is therefore an acceptable method of evaluating efficacy. It is, however, important to combine subjective wellbeing with attack rate records because a patient may so dislike one treatment period that he learns to reduce his activity and may return a record card showing similar attack rates to those in a treatment period in which his exercise tolerance was increased. It is sometimes forgotten that the purpose of an anti-anginal trial based on outpatients is to improve the quality of the patient's life, and this cannot be properly assessed during an artificial hospital exercise test.

We found slight statistical differences between the two-week and four-week results. It became apparent that on transfer from an active agent to the placebo two or three days were needed for a worsening to occur. We therefore recommend that at least one week be allowed to preclude any carry-over effect from blurring the results. We have used only the results of the last two weeks for our final assessment.

Using subjective criteria we have shown tolamolol to be a potent anti-anginal agent and have confirmed propranolol's effectiveness.

OBJECTIVE DATA

Though acute exercise tests are not totally relevant to the everyday life of patients, under standardized conditions they form a useful part of the assessment of anti-anginal therapy. The test we used had the advantages of rapid patient acceptance, reproducibility of end-point time and heart rate during the run-in assessment, ease of blood-pressure recording, and convenient monitoring by radiotelemetric electrocardiographic control (Holter, 1957).

When the heart rate rises the myocardial oxygen requirement also rises, and this relationship is almost linear (Andersen *et al.*, 1971). Adrenergic beta-receptor antagonism reduces myocardial oxygen consumption mainly by reducing the heart rate (Balcon, 1971) and systemic arterial pressure. Propranolol is apparently more effective in reducing the resting heart rate and tolamolol in reducing the blood pressure. Cardioselective adrenergic beta-receptor antagonists are less effective in reducing the resting heart rate because of their lack of effect on peripheral vasodilatation (Barrett, 1971). Practolol also possesses intrinsic sympathomimetic activity which decreases further its effect in reducing the heart rate. While tolamolol causes less slowing of the resting heart rate than propranolol, as one would expect from its cardioselective properties, it increases its anti-anginal efficacy by decreasing arterial pressure to a greater degree ($P < 0.05$). Tolamolol 100 mg thrice daily in comparison with practolol significantly ($P < 0.01$) reduces the resting heart rate, which probably reflects tolamolol's lack of intrinsic sympathomimetic activity and in turn its greater anti-anginal efficacy.

As tolamolol 200 mg thrice daily is as effective as propranolol in reducing the exercise heart rate and superior ($P < 0.05$) in reducing Robinson's index it appears that to base the degree of adrenergic beta-receptor antagonism entirely on the reduction of the resting heart rate is unreliable. A more accurate assessment of adrenergic beta-receptor antagonism can be made only from exercise observations, the most important being the reduction of peak exercise heart rate to below 110 beats a minute. This is particularly important when failure of adrenergic beta-receptor antagonism is considered a criterion for coronary arterial surgery.

The correlation of S-T segment changes with ischaemia is a subject of debate (Sandler, 1971; Livesley *et al.*, 1973; Thadani *et al.*, 1973). Thirty-seven of our patients had the same degree of exercise S-T depression in the placebo periods. A significant lessening of S-T depression on exercise occurs with adrenergic beta-receptor antagonists (Thadani *et al.*, 1973). Again, we have shown tolamolol and propranolol to be highly effective in reducing S-T depression, with tolamolol 200 mg having the lowest ranking. Depression of the S-T segment was increased to a greater degree when the exercise end-point was angina rather than breathlessness but no statistically significant difference was observed. If S-T segment changes indicate myocardial ischaemia (Reid *et al.*, 1971) then, these drugs may provide some anti-ischaemic effect irrespective of their pain-relieving role.

Conclusion

We have assessed subjective and objective criteria in 42 patients with angina pectoris and shown that tolamolol is an effective anti-anginal agent. The effectiveness of propranolol was confirmed. Initially we assumed tolamolol 100 mg thrice daily to be equipotent with propranolol 80 mg thrice daily. Though on some indices this may appear to be so, overall tolamolol 200 mg thrice daily appears to be equipotent with propranolol 80 mg thrice daily. Though we have shown practolol to have some anti-anginal effect, on final analysis no patient preferred it for long-term treatment and tolamolol 100 mg thrice daily was superior.

When anti-anginal efficacy was analysed propranolol was found to have a greater effect than tolamolol in lowering the resting heart rate, and tolamolol a greater effect than propranolol

in reducing blood pressure. The latter warrants further study in hypertensive patients.

Tolamolol is a potent anti-anginal agent, preferable to practolol, and as effective as propranolol, but unlike propranolol it has the advantage of being cardioselective.

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Relationship of Posture and Age to Urinary Protein Excretion

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Summary

The influence of posture and age on urinary protein excretion was studied in 120 normal men volunteers. The supine excretion rate was less than 140 $\mu\text{g}/\text{min}$ in all but two people (median value 38 $\mu\text{g}/\text{min}$) and tended to increase with age. The excretion rate decreased on quiet standing in 80% of people, which corresponded to a fall in creatinine clearance. In the remaining 20% protein excretion increased on standing but generally remained within normal limits and was dissociated from changes in creatinine clearance. This increase was more prevalent in younger people and may represent a phenomenon analogous to orthostatic proteinuria, differing only quantitatively.

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Introduction

Since abnormal amounts of protein in the urine probably indicate renal disease it is important to know the normal range of protein excretion. Wide variations in the upper limit of normal (Savory *et al.*, 1968) reflect not only the different methods of measuring total protein but also inherent inaccuracies in urine collections and the effect of factors such as posture, exercise, exposure to heat or cold, and emotional stress. We report here a study in which we tried to clarify the picture by eliminating some of these variables by standardizing the procedure (Pillay *et al.*, 1972) and by relating protein excretion to posture and age.

Subjects and Methods

The 120 healthy male volunteers studied were allocated to one of three groups of 40 according to their age. Group 1 (24-36 years) consisted mainly of interns and residents, group 2 (18-23 years) of college students, and group 3 (11-17 years) of schoolchildren. Women were excluded because of difficulties in obtaining uncontaminated urine.

All volunteers were studied in a room under the close supervision of an attendant. Each test was preceded by an equilibration period of lying supine for 15 to 30 minutes, at the end of which urine was collected and discarded. Each person then lay supine for one hour and spent a second hour standing quietly in an easy but not deliberately lordotic or kyphotic posture. Gentle walking was allowed during the period of standing. Each person drank 200 ml of water at the beginning of each period. Urine was collected at the end of each period by voiding. Blood for analysis was taken halfway through the study from people in groups 1 and 2 but not from those in group 3. Two